Amendments to the Specification:

Please amend the specification as follows:

Please cancel the previous version of the abstract and replace it with the substitute abstract on the following page:

Page 11, line 10, insert the following new paragraphs before the paragraph beginning on line 10:

Fig. 1C illustrates a snap-shot of a sample of a chemical compound information table in the chemical compound database showing certain entries and formats for entering consistent information in tables according to one embodiment of the present invention;

Fig. 1D illustrates certain components of databases comprising one embodiment of the present invention and identifying certain compound sets in the chemical compound database as being or not being of chemical synthetic origin;

Page 11, line 13, insert the following new paragraph before the paragraph beginning on line 13:

Fig. 2A illustrates a database record of an amino acid sequence and multidimensional organizational descriptors for a molecular target according to one embodiment of the present invention;

Page 11, line 15, insert the following new paragraph before the paragraph beginning on line 15:

Fig. 3A illustrates a snap-shot of a sample of a biological activity information table in the biological activity database segment showing certain entries and formats for entering consistent information in tables according to one embodiment of the present invention;

Page 11, line 8, insert the following new paragraphs:

Fig. 7A illustrates a graphical representation of results of tests of interactions between a multiplicity of selected chemical compounds and a selected molecular target in the form of a chemical profile.

Fig. 7B illustrates a graphical representation of results of tests of interactions between a multiplicity of selected chemical compounds and a different selected molecular target.

Fig. 7C illustrates a graphical representation of results of tests of interactions between a multiplicity of selected chemical compounds and a multiplicity of selected molecular targets, as one embodiment of the present invention.

Fig. 8A illustrates a graphical representation of results of tests of interactions between a selected chemical compound and a multiplicity of molecular targets in the form of a molecular target profile.

Fig. 8B illustrates a graphical representation of results of tests of interactions between a multiplicity of selected known bioactive chemical compounds and a multiplicity of molecular targets, as one embodiment of the present invention.

Page 15, replace the paragraph beginning on line 7 with the following new paragraph:

n) Davies, K. and Upinn, R., 3D pharmacophore searching, Net. Sci., (http://www.netsci.org/Science/Cheminform/feature02.html);

Page 15, replace the paragraph beginning on line 9 with the following new paragraph:

o) Golender, V. and Vesterman, B., APEX 3D expert system for drug design, Net. Sci. (~~http://~~www.awod.com/netsci/Science/Compchem/feature09.html);

Page 16, before the first paragraph, insert the following new paragraph:

Of particular relevance from these incorporated references are data mining and statistical tools, algorithms, and data interrogation methods and approaches that can be employed to organize, store, retrieve, compare and query the content of the database and generate predictions useful for drug discovery and development. These diverse tools, methods and approaches applicable to the present invention range from recursive partitioning, to molecular conformation and alignment, to three-dimensional structure-activity relationships, to comparative molecular field analysis, and to simulation technology. Useful statistical interrogation algorithms are well known to those who are skilled in the art of statistical analysis, and may include but is not limited to, recursive partitioning, single or multiple linear regressions, or Monte Carlo analysis.

Page 17, replace the paragraph beginning on line 19 with the following new paragraph:

(a) Compounds that are pharmacological reference agents or reference standards for measuring the interaction or molecular binding between unknown chemical compounds and a specific molecular target, such as a receptor or enzyme. Examples of such reference compounds include those compounds that are used for

characterizing binding interactions between test compounds and molecular targets including receptors or enzymes. <u>A partial compilation of representative reference agents and related known bioactive compounds, for example, is contained in the Examples at the end of the description below.</u> Other reference agents could include chemicals selected from the catalog of Research Biochemicals Inc. (RBI), a unit of Sigma Aldrich Corp., <u>including those chemicals listed under its LOPAC product (see Examples)</u> and from other sources that are well known in the industry. These pharmacological reference compounds often have been tested previously and/or marketed as pharmaceuticals or are natural products with characterized biological activity and therefore may overlap with compounds in the following three categories;

Page 19, line 17, insert the following new paragraph before the paragraph beginning on line 17:

A group of representative chemical compounds that can be included in the chemical compound database is provided in the Examples. These chemicals are primarily reference agents for pharmacological assays relevant to drug discovery and development, which one skilled in the art can readily recognize from the structures provided for each compound as primarily synthetic, drug-like chemical compounds, although other compound types are included within embodiments of this invention. For each compound in the Examples, information regarding known bioactivity with respect to certain molecular targets is presented. In one embodiment, an additional database is provided consisting of the results of tests to determine the interaction of each such compound with each of a multiplicity of other molecular targets, or results of tests of the

effect of each such compound on the interaction between a different compound known to interact with a specific molecular target and that target. Another particularly relevant collection of information-rich chemicals with known bioactivity that could be included in the chemical compound database is LOPAC (List of Pharmacologically Active Compounds), a listing of which is contained in the Examples.

Page 19, replace the paragraph beginning on line 17 with the following new paragraph:

For each compound included in the database, chemical structure, chemical formulae, physical chemical characteristics, chemical space coordinates or other chemical structure descriptors (*e.g.*, Smiles codes), solubility, and other relevant data, to the extent such information is available, are entered into fields in the database. Of particular relevance, the chemical descriptors could include two dimensional (2-D) topological descriptors, such as atom pairs, topological torsions, and atom triplets, which are generated from the molecular topology and used to represent the structural features of chemical compounds (Chen, et al.). Such 2-D descriptors can be used particularly with data mining methods such as recursive partitioning. Other chemical features that may be described and entered in the database include but are not limited to descriptors of distance geometries, such as the atom pair distance, either through-bond (2D) or through-space (3D); or descriptors of physical parameters like charge or Van der Waals distributions; or descriptors of physical-chemical characteristics such as hydrogen-bond acceptors or donors; or descriptors of chemical functional groups, such as methyl, carbonyl, or amide; or descriptors of chemical moieties, such as aryl or alkyl.

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<u>They could also include molecular fragments such as linear regression fragments.</u> Those skilled in the art would recognize other parameters that might be included. Chemicals can be organized by chemical structure relatedness in the database or in other relationships.

Page 20, after the last line of the page, please insert the following new paragraphs:

Fig. 1C illustrates one form of a table in the chemical compound database, for example, that may include database entries for properties and/or descriptors associated with each chemical compound, including Hammett Sigma value, Smiles code, and factors related to the drug-like nature of small molecule synthetic chemicals, such as number of rotatable bonds, Log P value, molecular weight, and other parameters. The bottom of the table shows selectable tables and tabs for data entry validation to ensure consistency of entries in the database, especially for text entries.

Fig. 1D illustrates selected subcomponents of the multi-component database including (a) the biological or target database, which especially includes drug discovery and development-related targets; (b) the chemical compound database, which can include as a subset bioactive chemicals and known drugs that are generally known in the art to be synthetic chemicals, or which in certain embodiments can include natural products that are not entirely from chemical synthetic origin; and (c) a biological activity database component related to information about drug efficacy, side effects and toxicology of the chemicals included in the subset of the chemical compound database containing the known drugs and related bioactive chemicals.

Page 22, please replace the paragraph beginning on line 4 with the following paragraph:

Enzymes can include proteases, carbohydrases, kinases, phosphatases, DNA-modifying enzymes, transferases, P450's, and others known to those skilled in the art, including those listed in greater detail below.

Page 22, please replace the paragraph beginning on line 6 with the following paragraph:

Other receptors, receptor sources, and corresponding assays are constantly being developed by the Assignee to be added to the content of the database. Additional receptors and receptor assays are well known to those skilled in the art. Lists and descriptions of certain receptors relevant to drug discovery and development can be found in numerous publications known to those skilled in the art. These publications include the RBI Handbook of Receptor Classification and Signal Transduction, 3rd Edition, Kenneth J. Watling, Ph.D., Natick, MA (the "RBI Handbook"), and the IUPHAR receptor classification book. Numerous representative receptors are identified in the Examples below, which also includes selected assay protocol information for each of the molecular targets identified that can be used, as one of any number of possible test methods, to determine or measure interactions between compounds and molecular targets for purposes of creating an additional database containing results of tests of interactions. Other types of receptors identified in the RBI Handbook that may be relevant for inclusion in the molecular targets database, includes the following: nicotinic

receptors, metabotropic glutamate receptors, prostanoid receptors, P2Y receptors, bombesin receptors, chemokine receptors, cytokine receptors, galanin receptors, melanocortin receptors, proteinase activated receptors, somatostatin receptors, vanilloid receptor, steroidal intracellular receptors, and non-steroidal intracellular receptors. ~~Furthermore, as new receptors and receptor subtypes are discovered, they can be added to the content of the database.~~

Page 22, line 14, insert the following new paragraph before the paragraph beginning on line 14:

As is customary and known for those skilled in the field, and as included in the RBI Handbook, the term "receptor" can more broadly encompass related types of molecular targets that bind ligands. These include, for example, transporters, which in turn includes biogenic amine transporters such as dopamine transporter, norepinephrine transporter, serotonin transporter, and vesicular monoamine transporters and excitatory amino acid transporters such as EAAT1-5; ion channels including calcium channels, chloride channels, potassium channels, and sodium channels; and ligand-gated ion channels such as nicotinic acetylcholine receptors, GABA A receptors, glutamate receptors in the ion channel family, the glycine receptor, and nucleotide P2X receptors. One other form of molecular target included within the broad scope of receptor or ligand-binding targets, as also described in the RBI Handbook, is targets that mediate signal transduction events or secondary messenger effects upon binding of a certain compound (an agonist) to, and functional activation of, cell surface receptors, such as for example, G Protein Coupled Receptors. These

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receptor signal transduction molecular targets include heterotrimeric G proteins, which mediate effectors such as adenyl cyclase (through cAMP), phospholipase C, Ca^{++} channels, K^+ channels or certain kinases, and InsP3 (inositol triphosphate) as well as ryanodine receptors. Furthermore, as new receptors and receptor subtypes and other relevant molecular targets are discovered, they can be added to the content of the database.

Page 22, please replace the paragraph beginning on line 14 with the following paragraph:

Enzymes and enzyme assays are well known to those skilled in the art. Listings, descriptions, and related information on selected enzymes of relevance to drug discovery and development that may be included within the molecular targets database are also found in the RBI Handbook. These include caspases 1-11; cyclic nucleotide phosphodiesterases such as PDE 1-7 and 9; enzymes involved in acetylcholine synthesis and metabolism such as choline acetyl transferase and acetylcholinesterase; enzymes involved in dopamine, norepinephrine, and epinephrine synthesis and metabolism such as tyrosine hydroxylase, monoamine oxidase, catechol-O-methyltransferase, alcohol dehydrogenase, and aldehyde reductase; enzymes involved in histamine synthesis and metabolism; neuropeptidases such as neurolysin, aminopeptidases N, A, B, P, proline endopeptidase, carboxypeptidases, NAALA dipeptidase, etc.; nitric oxide synthases; phospholipase A2; phospholipase C; phospholipase D; phosphoprotein phosphatases such as PP1, PP2A, PP4, PP5, PP2B, PP2C, VH1 group, cdc25 group, and tyrosine phosphatases; protein prenyltransferases;

serine/threonine kinases such as cAMP-kinase (PKA), cGMP-kinase (PKG), Protein Kinases C, RAC/Akt/PKB, G Protein Coupled Receptor Kinases (GRKs), p70-s6 kinase, p90-s6 kinase, calcium/calmodulin-regulated protein kinases (CaMK), MAPKAP-K2 and K3, Mnk, cyclin dependent kinases, MAP kinases (ERKs), JNK (SAPK1, p38 (SAPK 2,3), GSK3, casein kinase, MEK1/MEK2, MEKK, Raf, Pak, CK1, TGF, Activin; receptor-linked tyrosine kinases such as EGFR, Her-2/neu/c-erbB2, PDGFR, IGF-1R, and FGFR; and non-receptor linked tyrosine kinases such as src family, Bcr-Abl, and Jak-2/Jak family. Lists and descriptions of certain receptors relevant to drug discovery and development can be found in numerous other publications known to those skilled in the art.

Page 22, line 17, insert the following new paragraph before the paragraph beginning on line 17:

Furthermore, one skilled in the art will recognize that other assay protocols and other detection methods, including but not limited to fluorescence assays, time-resolved fluorescence assays, fluorescence polarization assays, ELISAs, RIAs, reporter gene assays, etc, may also be used within the framework of this invention to generate binding or molecular interact data.

Page 23, please replace the paragraph beginning on line 7 with the following paragraph:

In table 410, column 411 contains the name of the receptor, which is also the name of the target in column 401 in table 400; column 412 includes receptor family

information; column 413 includes receptor superfamily information; column 414 includes receptor subfamily information; column 415 includes the information about the degree of homology of the DNA sequence of corresponding genes; and column 416 includes information on amino acid sequence. The amino acid sequence is one of a number of molecular descriptors that may be included in the database. Other molecular descriptors, for example, could include hydropathy plots corresponding to the amino acid sequence[[.]] , spatial distribution of structural features such as the number of helices of transmembrane domains, location of beta sheets, and linear and three-dimensional representations of the structure of the molecular target. Fig. 2A shows, for example, a database record of an amino acid sequence for a seven trans-membrane (7TM) molecular target that is arranged with identification of segments associated with helices forming the trans-membrane regions and other regions (including those containing sheet configurations) that comprise the extra-membrane loops. Because the molecular target database represented by tables 400, 410, and 420 includes target information and associated biological information related to the targets is included in the database (see table 600), this database may be considered a two-component database. The columns shown are illustrative of the types of information that may be included in the database and should not be constructed as limiting the invention.

Page 26, line 9, insert the following new paragraph:

Fig. 3A shows an example of one possible biological activity information table in the biological activity database component that contains fields for entry of information on animal model and human data, teratogenicity, mutagenicity, reproductive toxicology,

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metabolites, etc., and in the lower section of the database record shows tabs and formats for entering internally consistent and comparable information in the tables as one embodiment of the present invention.

Page 29, line 12, insert the following new paragraphs before the paragraph beginning on line 12:

Tests or assays are developed and utilized to generate binding, reactivity, or other interaction data for each specific molecular target included in the database. Representative assay protocol summaries for more than 150 different assays for molecular targets, including receptors, transporters, ion channels, enzymes, and cell signaling molecules, are shown in the Examples. For these protocols, examples are provided of selected labeled ligands, including radioligands, that are known to bind to the molecular target at sites that are functionally relevant for drug discovery and development purposes. These labeled ligands, or radioligands, represent one form of compound known to interact with the (respective) molecular target. Other compounds, such as those from the chemical compound database, can be tested for their effect on this interaction between the compound known to interact (the labeled ligand or radioligand) and the molecular target.

The interaction between the test compound and the molecular target, for example, can be to bind to the molecular target and compete with or displace the labeled ligand or radioligand from its binding site on the molecular target. These assays may therefore measure binding as one indicator of interaction between the molecular target and chemical compounds included in the database. As is well known to those in

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the art, binding of a chemical compound to a functional site on a target, for example the site to which the labeled- or radio-ligand binds on a receptor according to many of the assay protocols in the Examples, may lead to either functional activation (agonist activity) or functional inhibition (antagonist activity), with respect to the molecular target. Tests or assays to measure interaction may be designed to evaluate functional activity. For example, in the Examples, test protocols are presented for measuring interactions both in the form of binding to the molecular target adenosine transporter and in the form of functional transport by the adenosine transporter. Different assay protocols can be designed for measurement of different forms of interaction. In the case of the adenosine transporter binding and functional assays, different radioligands are used, and in this example the functional assay measures the effect of a test compound on the ability of the adenosine transporter to transport a known compound, radiolabeled adenosine, across the cell membrane without the test requiring measurement of direct binding activity.

Multiple types of screening assays for the same molecular target to measure different forms of interaction between compounds and targets in the database may be utilized. In particular, assays related to targets involved in cell signaling, such as adenyl cyclase and inositol triphosphate (see Examples for selected assay protocols; other test methods can be used), both of which are linked to downstream signaling events following functional activation of G-Protein Coupled Receptors (GPCRs), may be used. Assays for measuring interactions between compounds and targets with respect to functional activity of GPCRs may include measurement of activation (agonists) or inhibition of activation (antagonists), both of which are mediated by binding between the

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test compound and molecular target. Such assay methods are well known to those familiar with the art, and pharmacological parameters related to such functional interaction measurements, including agonist and antagonist information for each specific molecular target, are also included in the RBI Handbook.

Page 33, line 3, insert the following new paragraphs before the paragraph beginning on line 3:

A user interface can be used to selectively view records of tests of interactions between chemical compounds and molecular targets. The chemical profile representing results of tests of selected compounds from the first database can be viewed for a selected molecular target, as shown in Fig. 7A for the molecular target serotonin receptor subtype 5HT-3 and 20 selected compounds, with interaction information represented as % inhibition of binding by the test compounds with respect to a compound known to interact with the 5HT-3 receptor. Similarly, the same type of chemical profile can be viewed in Fig. 7B for interactions between 48 selected compounds and the serotonin receptor subtype 5HT-4. Records of interaction data can further be viewed for a multiplicity of molecular targets and multiplicity of chemical compounds selected from the databases. Fig. 7C shows interaction data that can be viewed and compared for a set of 20 compounds and two targets, 5HT-3 and 5HT-4. Fig. 7C could be extended to show interaction test records for N chemical compounds from table 300 and M molecular targets from table 400 to demonstrate a multidimensional database that is one embodiment of the present invention.

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Alternatively, a user interface can be used to view records of tests of interactions between chemical compounds and molecular targets in the format of one chemical compound tested for interactions with a multiplicity of molecular targets to show a molecular target profile. Fig. 8A shows such a view for the chemical compound alprenolol, which is a known bioactive compound and marketed pharmaceutical, tested against 56 molecular targets, with test results indicated in terms of % inhibition. Fig. 8B extends the view to include two compounds, alprenolol and albuterol, tested against 40 molecular targets (receptors, including ion channels and transporters). Fig. 8B could also be extended to show interaction test records for N chemical compounds from table 300 and M molecular targets from table 400 to demonstrate a multidimensional database that is one embodiment of the present invention.

Such datasets of chemical profiles or molecular target profiles can be components of a database containing table 200 screening results and entered into table 710 logical tables and queried by data mining methods to form the basis of using the database 100 for predicting the drug potential of a new compound, as one embodiment of the present invention.

Page 33, after the last line, please insert the following new pages, starting on the following page of this Amendment (pages 19-262):